CD

THE SYNTHESIS OF 5-ALKYLAMINOMETHYLTHIENO[2,3-b]PYRROLE-5-SULFONAMIDES

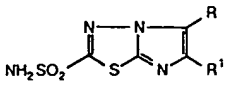
George D. Hartman* and Wasyl Halczenko

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania, 19486, U.S.A.

Abstract - Novel 2-aminomethylthieno[2,3-b]pyrrole-5-sulfonamides have been prepared by direct chlorosulfonation/amidation of N-protected intermediates.

Aryl sulfonamides have recently been shown to be effective agents for reducing the intraocular pressure in rabbits after topical administration[1-3] and are thus under clinical study in the treatment of ocular hypertension. The mechanism of action of these molecules appears to involve inhibition of carbonic anhydrase with resultant diminution in aqueous humor formation.[4,5] As part of our program to develop potent, topically effective carbonic anhydrase inhibitors[6,7] we wish to report the synthesis of novel, water soluble aminoalkyl derivatives of thieno[2,3-b]pyrrole-5-sulfonamides. This effort employs a novel protection-deprotection scheme for the pyrrole nitrogen and a highly efficient electrophilic aromatic chlorosulfonation as the key step.

Among the various aryl sulfonamides which have shown potent inhibition of carbonic anhydrase activity,[1,6,7] the imidazo[2,1-b]thiadiazole sulfonamides[8] 1 were of interest to us because of their pharmacologic profile. Specifically we were interested in the effect on biological activity of modifying the nitrogen atom site of a fused [5.5] heterocycle to be a hydrogen donor moiety rather than the acceptor that it is in 1.

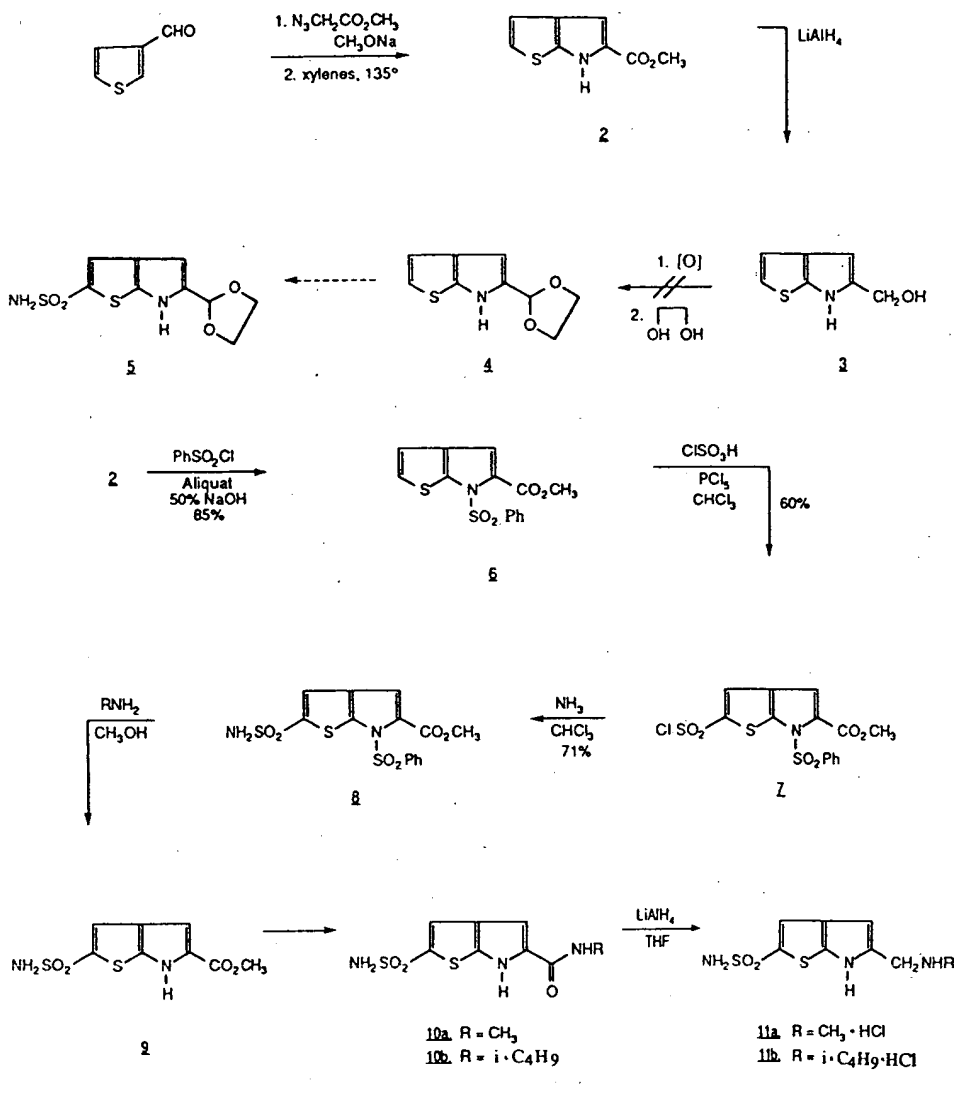


1

We therefore undertook the preparation of thieno[2,3-b]pyrrole-5-sulfonamides IIa and IIb, which possess an aminoalkyl function to enhance water solubility.

Although the parent thieno[2,3-b]pyrrole is not stable to air or light,[9,10] it was expected that the required sulfonamide 9 should be an isolable compound due to the presence of appropriate electron-withdrawing functionality. This has proven to be the case and the synthetic pathway to this system is shown in Scheme I.

Scheme I


CHO
1. $N_3CH_2CO_2CH_3$
CH_3ONa
2. xylenes, 135°
CO_2CH_3
LiAlH$_4$
2
1. [O]
2. OH OH
CH_2OH
3
4
NH_2SO_2
5
$PhSO_2Cl$
Aliquat
50% NaOH
85%
SO_2Ph
6
$ClSO_3H$
PCl_5
$CHCl_3$
60%
RNH_2
CH_3OH
NH_3
$CHCl_3$
71%
Cl SO_2
7
8
9
NHR
10a R = CH_3
10b R = i·C_4H_9
LiAlH$_4$
THF
CH_2NHR
11a R = CH_3·HCl
11b R = i·C_4H_9·HCl

Treatment of thiophene-3-carboxaldehyde with methyl azidoacetate followed by thermolysis provided methyl thieno[2,3-b]pyrrole-2-carboxylate (2).[12] The original plan involved reduction of 2 to the alcohol 3, followed by oxidation to the aldehyde stage and protection to give 4. It was further anticipated that metallation at the carbon α to the sulfur followed by sulfonylation would afford the appropriately functionalized sulfonamide 5. In practice, although lithium aluminum hydride reduction of ester 2 gave 3 in high yield, oxidation of carbinol 3 under a variety of conditions resulted only in complex mixtures.

Reasoning that the hydrogen-substituted pyrrole nitrogen was the source of our synthetic difficulties, we decided at this stage to protect this function with the phenylsulfonyl group.[13] This was readily accomplished in high yield at room temperature by treatment of 2 with phenylsulfonyl chloride under phase-transfer conditions[14] to provide 6. Thus, although selective reduction of the ester followed by metallation and sulfonylation as previously described appeared to be a viable route, we opted to investigate direct electrophilic aromatic sulfonylation. Although little is known about the reactivity of the thieno[2,3-b]-pyrrole nucleus in this sense, and recognizing that the phenylsulfonyl function would diminish nucleophilic potential, the exceptional performance of analogous [5.5] fused systems in electrophilic substitution reactions[15,16] suggested a favorable outcome. Treatment of 6 in chloroform solution at 0-10° under standard chlorosulfonating conditions provided, after hydrolytic work-up, the desired chlorosulfonated derivative 7 in 60% yield. Interestingly, attempted chlorosulfonation of 2 under similar conditions resulted only in decomposition. Ammonolysis of 7 with ammonia in chloroform gave sulfonamide 8 in good yield, while treatment of 7 in acetone with ammonium hydroxide provided a more complex product mixture. At this point we anticipated that conversion of 8 to final amine products IIa and IIb would involve three steps: amidation of the ester, reduction of the amide, and basic hydrolysis of the phenylsulfonyl protecting group. However, upon treatment of 8 with methanolic methylamine containing sodium methoxide or with methanolic isobutylamine, the phenylsulfonyl group was rapidly cleaved to give 9 which was slowly converted under the above conditions to the required amides 10a and 10b, respectively. Although desulfonylation in the present case diminished the rate of amidation, this deprotection of the pyrrole nitrogen with a primary amine constitutes a much milder method for this transformation than the basic hydrolytic techniques currently cited.[13] The synthesis was completed by treatment of 10a and 10b with lithium aluminum hydride in refluxing tetrahydrofuran solution over the course of several days to provide the hydrochloride salts IIa and IIb, respectively.

In summary we have prepared novel 2-aminomethylthieno[2,3-b]pyrrole-2-sulfonamides by a mild chloro-sulfonation/amidation sequence which employs an efficient protection-deprotection scheme for the pyrrole nitrogen. We expect that these concepts will have general application in the synthesis and transformations of similar fused [5.5] systems.

EXPERIMENTAL

Melting points are uncorrected and were taken in air with a Thomas-Hoover capillary apparatus. The nmr spectra were recorded on an EM-390 or a Nicolet NT-360 spectrometer with TMS as internal standard.

Methyl thieno[2,3-b]pyrrole-2-carboxylate (2).

This compound was prepared according to Soth et al.[12] in 52% overall yield from thiophene-3-carboxaldehyde.

Thieno[2,3-b]pyrrole-2-carbinol (3).

To a suspension of 5.66 g (0.15 mol) of lithium aluminum hydride in 150 ml of ether cooled to 0-10° C under nitrogen was added a solution of 13.5 g (0.075 mol) of 2 in 200 ml of ether dropwise over 15 min. The resulting suspension was stirred at 0-10° C for 2.5 h and was then hydrolyzed by the sequential addition of 5.66 ml of water, 5.66 ml of 15% NaOH solution, and 17.0 ml of water with stirring for 1 h. The white solid was filtered off and the solvent was removed in vacuo. The resulting oil was dissolved in chloroform and passed through a silica gel pad. Solvent removal provided 9.6 g (85%) of 3 (homogeneous on tlc, R_f 0.4 with 5% ethyl acetate/hexane), as a clear oil; nmr (deuteriochloroform): δ 4.57 (2H, b s), 6.29 (1H, d, J = 2 Hz), 6.80 (1H, d, J = 8 Hz), 6.93 (1H, d, J = 8 Hz), 8.70 (1H, b s, OH).

Methyl 1-phenylsulfonylthieno[2,3-b]pyrrole-2-carboxylate (6).

To a mechanically stirred mixture of 0.5 g (2.76 mmol) of 2, 1.4 g (2.76 mmol) of Aliquat-336, and 1.0 g (5.68 mmol) of phenylsulfonyl chloride was added 5 ml of a 50% aqueous sodium hydroxide solution at room temperature. After stirring for 0.5 h, the reaction mixture was diluted with 25 ml of water/50 ml of chloroform. The organic phase was separated, washed with 3 x 20 ml portions of water, brine, and dried over sodium sulfate. The solution was passed through a silica gel pad and the solvent was removed in vacuo to give a semi-solid. This was triturated with cold hexane and filtered to give 0.75 g (85%) of 6 as a tan solid recrystallized from ether/hexanes, mp 165-167° C; nmr (deuteriochloroform): δ 3.68 (3H, s), 7.00 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.29 (1H, s), 7.59 (3H, m), 8.06 (2H, d, J = 8, 1 Hz); ms: m/z 321.

Methyl (1-phenylsulfonyl-5-chlorosulfonyl)thieno[2,3-b]pyrrole-2-carboxylate (7).

To a solution of 0.52 g (2.5 mmol) of phosphorus pentachloride in 0.73 g (6.3 mmol) of chlorosulfonic acid under nitrogen and cooled to 0-10° C was added a solution of 0.80 g (2.5 mmol) of 6 in 10 ml of chloroform dropwise. After stirring for 0.5 h the reaction mixture was quenched with ice and was then extracted with 4 x 25 ml portions of chloroform. The combined organic phases were washed with brine, dried over sodium sulfate and the solvent was removed in vacuo to give an amber oil. This was triturated with ether to provide 0.60 g (60%) of 7 as a tan solid recrystallized from ethyl acetate/hexanes, mp 175-180° C dec; nmr (deuteriochloroform): δ 3.80 (3H, s), 7.39 (1H, d, J = 1 Hz), 7.60 (2H, t, J = 7 Hz), 7.72 (1H, t, J = 5 Hz), 7.90 (1H, s), 8.10 (2H, dd, J = 8, 1 Hz); ms: m/z 419.

Methyl (1-phenylsulfonyl-5-sulfamoyl)thieno[2,3-b]pyrrole-2-carboxylate (8).

Gaseous ammonia was bubbled into a solution of 5.10 g (12.0 mmol) of 7 in 250 ml chloroform cooled to 0-10° C for 10 min. The reaction mixture was stirred for 0.5 h and then the solvent was removed in vacuo. The residue was taken up in 100 ml of ethyl acetate/50 ml of water. The organic phase was

separated, washed with water, brine, dried over sodium sulfate and passed through a silica gel pad. The solvent was removed in vacuo to provide 3.84 g (71%) of 8 as a white solid homogeneous by tlc, R_f 0.4 with 10% methanol/chloroform, mp 197-199° C; nmr (DMSO-d_6): δ 3.72 (3H, s), 7.55 (1H, d, J = 2 Hz), 7.79 (3H, m), 7.85 (3H, m), 7.98 (2H, dd, J = 8, 1 Hz); ms: m/z 301.

N-Methyl 5-sulfamoylthieno[2,3-b]pyrrole-2-carboxamide (10a).

Gaseous monomethylamine was bubbled into 40 ml of methanol cooled to 0-10° C for 10 min. To this was added 3.0 g (7.5 mmol) of 8 followed by 5 mg of sodium metal and the resulting solution was stirred under nitrogen for 4 days. The solvent was removed in vacuo and after adding 50 ml of water, the pH was adjusted to 8-9 with 6N HCl. Upon cooling and stirring at 0-10° C a tan solid appeared. This was collected and washed with water to give 1.85 g (95%) of 10a, homogeneous by tlc, R_f 0.6 with 10% methanol/chloroform, mp > 260° C (dec); nmr (DMSO-d_6): δ 3.32 (3H, s), 7.05 (1H, d, J = 2 Hz), 7.55 (3H, m), 8.31 (1H, m).

2-(Methylamino)methylthieno[2,3-b]pyrrole-5-sulfonamide hydrochloride (11a).

To a suspension of 1.37 g (0.036 mol) of lithium aluminum hydride in 150 ml of THF at room temperature was added 1.56 g (0.006 mol) of 10a in 150 ml of THF dropwise and the resulting mixture was heated at reflux. After 22 h the reaction mixture was cooled and quenched with 50 ml of a saturated Na^+-K^+ tartrate solution. After adjusting the pH of this mixture to 8-9 with dilute HCl, it was extracted with 5 x 200 ml portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and the solvent was removed in vacuo. The residue was taken up in 3N HCl (50 ml) and extracted with ethyl acetate to remove the unreacted 10a. The aqueous phase was rendered basic (pH 8-9) with 1N NaOH solution and extracted with 5 x 50 ml portions of ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and the solvent was removed in vacuo to provide the free base of 11a as a yellowish solid (0.25 g, 17% yield). This material was converted to 11a by treatment with excess ethanolic HCl in a mixture of EtOH (15 ml)-MeOH (5 ml) to provide 0.15 g of 11a as a tan solid. Recrystallization from ethanol gave material with mp 210-212° C (dec), nmr (DMSO-d_6): δ 1.50 (3H, d, J = 9 Hz), 4.20 (2H, b s), 6.58 (1H, d, J = 2 Hz), 7.49 (1H, s), 7.53 (2H, b s, SO_2NH_2), 9.00 (2H, b s, NH_2^+), 11.50 (1H, bs, NH). Anal. Calcd for $C_8H_{11}N_3O_2S$ HCl: C, 34.10; H, 4.29; N, 14.91. Found: C, 34.48; H, 4.52; N, 14.68.

N-Isobutyl 5-sulfamoylthieno[3,2-b]pyrrole-2-carboxamide (10b).

A solution of 3.0g (7.5 mmol) of 8 in 30 ml of isobutylamine was heated at reflux for 24 h. Excess amine was removed in vacuo and after the addition of 50 ml of water, the pH was adjusted to 8-9 with 1N HCl. This was extracted with 4 x 75 ml portions of ethyl acetate and the combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed in vacuo to give a yellow residue that was triturated with ether to provide 1.86 g (83%) of 10b as a white solid, recrystallized from methanol/chloroform, mp 247-252° C (dec); nmr (DMSO-d_6): δ 0.90 (6H, d, J = 8 Hz), 1.82 (1H, m), 3.08 (2H, t, J = 6 Hz), 7.14 (1H, d, J = 1 Hz), 7.56 (3H, m), 8.32 (1H, t, J = 8 Hz).

2-(Isobutylamino)methylthieno[2,3-b]pyrrole-5-sulfonamide hydrochloride (IIb).

To a suspension of 1.32 g (0.0348 mol) of lithium aluminum hydride in 150 ml of THF at room temperature was added 1.75 g (0.0058 mol) of 10b in 50 ml of THF dropwise and the resulting mixture was heated at reflux. After 48 h the reaction mixture was cooled and quenched with 50 ml of saturated Na^+-K^+ tartrate solution. After adjusting the pH of this mixture to 8-9 with 1N NaOH solution it was extracted with 3 x 200 ml ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and the solvent stripped. This residue was dissolved in 3N HCl (50 ml) and extracted with ethyl acetate to remove unreacted 10b. The aqueous phase was then made basic (pH 8-9) with 1N NaOH solution and extracted with 5 x 50 ml portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and the solvent was removed in vacuo to provide the free base of IIb as a yellowish solid. This was dissolved in warm ethanol and treated with ethanolic HCl (1 molar equivalent) to provide 0.46 g (28%) of IIb as a tan solid that was triturated with ether, mp 200-203° C (dec); nmr (DMSO-d_6): δ 0.90 (6H, d), 1.98 (1H, m), 2.70 (2H, b s), 4.26 (2H, b s), 6.61 (1H, d, J = 2 Hz), 7.49 (1H, s), 7.53 (2H, b s, SO_2NH_2), 9.10 (2H, b s, $-NH_2^+$), 11.65 (1H, b s). Anal. Calcd for $C_{11}H_{17}N_3O_2S_2$ HCl; C, 40.79; H, 5.60; N, 12.97. Found: C, 41.07; H, 5.64; N, 12.94.

ACKNOWLEDGEMENTS

The authors thank Dr. Robert L. Smith for his advice and encouragement throughout the course of this work. We also thank Dr. William C. Randall and his staff for microanalytical data, Dr. H. Ramjit for mass spectral determinations, and Mrs. Vera W. Finley for the typing of this manuscript.

REFERENCES AND NOTES

1. M. F. Sugrue, P. Gautheron, C. Schmitt, M. P. Viader, P. Conquet, R. L. Smith, N. N. Share, and C. A. Stone, J. Pharmacol. Exp. Ther., 1985, 232, 534.
2. T. H. Maren, L. Jankowska, G. Sanyal, and H. F. Edelhauser, Exp. Eye Res., 1983, 36, 457.
3. R. A. Lewis, R. D. Schoenwald, M. G. Eller, C. F. Barfknecht, and C. D. Phelps, Arch. Ophthalmol., 1984, 102, 1821.
4. T. H. Maren, Physiol. Rev., 1967, 47, 595.
5. T. H. Maren, Curr. Eye Res., 1985, 4, 399.
6. G. D. Hartman and W. Halczenko, J. Heterocyclic Chem., submitted.
7. G. D. Hartman and W. Halczenko, J. Heterocyclic Chem., submitted.
8. I. T. Barnish, P. E. Cross, R. P. Dickinson, B. Gadsby, M. J. Parry, M. J. Randall, and I. W. Sinclair, J. Med. Chem., 1980, 23, 117.
9. H. K. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, J. Amer. Chem. Soc., 1957, 79, 2556.
10. G. Kumar, K. Rajagopalan, S. Swaminathan, and K. K. Balasubramanian, Ind. J. Chem., 1981, 20B, 271.
11. M. Farnier, S. Soth, and P. Fournari, Can. J. Chem., 1976, 54, 1074.

12. S. Soth, M. Farnier, and C. Paulmier, Can. J. Chem., 1978, 56, 1429.

13. T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, N.Y., 1981.

14. V. Bocchi, G. Casnati, A. Dossena, and F. Villani, Synthesis, 1976, 414.

15. A. Bugge, Chem. Scripta, 1972, 2, 137.

16. V. P. Litvinov and Ya. L. Gol'farb, "Advances in Heterocyclic Chemistry", A. R. Katritzsky and A. J. Boulton (Eds.), Vol. 19, Academic Press, N.Y., p. 123, 1975.

Received, 5th June, 1989